Identifying markers for premature atherosclerosis in rheumatoid arthritis

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CHAPTER 1

Introduction

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General Introduction

Cardiovascular morbidity and mortality are increased in rheumatoid arthritis (RA) (1-3). Despite improved treatment of RA an increased incidence of cardiovascular diseases still remains, as is demonstrated by recent large cohort studies (4-6)Various causes of this increased prevalence have been proposed. Of these, traditional risk factors like smoking, hypertension, hyperlipidemia and increased body mass index (BMI) are involved (7-9). Also non traditional risk factors like oxidized LDL (ox-LDL), advanced glycation end products (AGEs) and auto-antibodies play a role (10).

Epidemiology

An increased risk for cardiovascular morbidity and mortality in RA has been shown. The nurses health study showed a twofold increase in myocardial infarction in women with RA, increasing to more than threefold when disease duration extended longer than ten years (11). In a large meta-analysis an increased mortality of 50% was found due to cardiovascular disease (CVD) in RA (1). Risk for myocardial infarction proved to be greater than that in type 2 diabetes mellitus (T2DM) in one study (12)

Markers for identifying premature atherosclerosis

Various markers are used for identifying premature atherosclerosis. Different stages of atherosclerosis are characterized by specific markers. These are extensively discussed in chapter two. The first stage is characterized by invasion of inflammatory cells into the vascular wall. Markers of this stage are, for example, serum levels of vascular cellular adhesion molecule-1 (sVCAM-1), von Willebrand factor (vWF) and thrombomodulin (TM). The second stage is characterized by endothelial dysfunction through further inflammation of the vascular wall. This leads to “stiffness” of the arterial wall, which is characterized by increased velocity of the pulse wave from the brachial artery to the radial artery. This increased velocity can be visualized by pulse wave analysis (PWA)(13). The increase in velocity is recalculated by a windkessel model to small artery elasticity (SAE). Finally the process leads to thickening of the vascular wall, as measured by intima media thickness (IMT). IMT is measured on the left and right side of the carotid bulb (CB), the internal carotid artery (ICA) and the common carotid artery (CCA). Increment of IMT in RA has been shown in several studies as compared to healthy controls (14, 15)

Aim and outline of the thesis

The main aim of the present thesis is (1) to identify markers for detection of early atherosclerosis in RA, and (2) to evaluate the effect of disease activity and treatment on early markers of atherosclerosis.

Introduction of the chapters

Chapter 2 discusses epidemiology and pathophysiology of cardiovascular disease in RA. Also methods for investigating the several stages of preclinical cardiovascular disease are discussed, such as markers for endothelial activation, endothelial dysfunction, IMT and advanced glycation endproducts (AGE's). Therapeutic strategies for minimizing cardiovascular risk are discussed in this chapter as well. This invited review (allowing limited number of references) was published in 2010 so covering the literature until that time.

Chapter 3 discusses a cross sectional study in 49 RA patients with established disease. We focused in this study on SAE. We hypothesized that the decrease in SAE in RA would be related to disease activity and markers of disease damage like the Sharp v.d. Heijde score, as well as to markers of endothelial activation and IMT.

In chapter 4 we cross-sectionally studied 49 RA patients with longstanding disease in comparison with sex and age matched healthy controls for the presence of AGE's. AGE's are the result of non-enzymatic oxidation and glycation of proteins and lipids under a hyperglycemic state or oxidative stress. Patients with long standing RA are supposed to have had longer periods of oxidative stress due to their disease. Here we related AGE's to markers of endothelial activation, such as sVCAM-1 and vWF, endothelial dysfunction as measured by small artery elasticity (SAE) and premature atherosclerosis as measured by IMT.

We hypothesized that in longstanding RA, AGE's are increased due to prolonged exposure to oxidative stress and as such, correlate with markers of disease damage. Futhermore we hypothesized that AGE accumulation is related to endothelial activation, endothelial dysfunction, and early atherosclerosis.

In chapter 5 we focus on angiogenic factors (angiopoietin-2 (Angpt-2) and vascular endothelial growth factor (VEGF)) in a cohort of 176 RA patients with established disease. This cohort was followed for 12.5 years and prevalence of CVD was retrieved from medical records.

As angiogenesis plays an important role in inflammation and, as such, possibly also in the development of atherosclerosis we analyzed angiogenic factors in relation to atherosclerosis in RA. Whether angiogenesis is a leading factor in inflammation or secondary to hypoxia in inflamed tissue is, however, still under debate (16) We here hypothesized that angiogenic factors would correlate with the development of CVD. Angpt-2, as well as VEGF and sVCAM-1, were measured at entry and after 2 years and were compared with levels in healthy controls (HC).

Chapter 6 concerns the role of endothelial progenitor cells (EPC's). EPC's are thought to play an important role in endothelial repair (17, 18) Depletion of EPC's might be related to defective endothelial repair, which could play a role in atherosclerosis. We studied an early RA cohort of 27 RA patients. EPC's were defined as CD133/CD34 positive cells by

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FACS analysis or by colony forming units by the Hill assay (19, 20). Numbers and function of EPC's were compared with that in age and sex matched healthy controls. Correlation with markers of endothelial activation and dysfunction as well as disease activity were studied.

In chapter 7 a longitudinal study is described in which 58 RA patients with a maximum disease duration of one year were treated with standard treatment consisting mainly of methotrexate, sulfasalazine and TNFα-blocking agents. We hypothesized that markers of endothelial dysfunction would be present before start of treatment and that disease activity would correlate with markers of early atherosclerosis. Also, we hypothesized that by reducing disease activity in the first year of treatment markers of premature atherosclerosis would decrease. Primary outcome in this study was endothelial function as measured by SAE. SAE was measured before initiation of therapy and after one year. Results found at entry were compared with that of age and sex matched healthy controls.

Secondary outcome measures were sVCAM-1 as an endothelial activation marker, intima media thickness and advanced glycation end products (AGEs). As mentioned premature markers for atherosclerosis were measured before start of treatment and after one year.

Finally, chapter 8 discusses a pilot longitudinal study in 15 RA patients with longstanding disease, who were treated with rituximab. We hypothesized that before rituximab treatment markers of premature cardiovascular disease would be present, and correlate with disease activity and that markers of premature cardiovascular disease would decrease after treatment. Primary outcome in this study was endothelial activation, as measured by sVCAM-1. Secondary outcome measures were endothelial dysfunction and IMT. Indication for treatment with rituximab in these patients was established by their own rheumatologist. After giving informed consent patients were included in the study. Before rituximab treatment markers of early cardiovascular disease were measured and compared with that of age and sex matched healthy controls. Four months after rituximab treatment measurements were repeated in the RA group. S-VCAM-1, SAE and IMT were related to disease activity.

All results are discussed in chapter 9 (Summary conclusions and future recommendations)

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